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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
FRIEND, TOMAS H F

ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 04/05/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary File Copy	Application No. 09/421,422	Applicant(s) HARBURY ET AL.	
	Examiner Tomas Friend	Art Unit 1627	

-- The MAILING DATE of this communication appears on the cover sheet with the c rresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *11-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Detailed Action

Change of Examiner

The examiner of this application has changed from Barba Koroma to Tomas Friend.

Status of the Application

Receipt is acknowledged of a response to an office action with amendment on 15 January 2002 (Paper No. 10).

Status of the Claims

Claims 1-14 are pending in the present application. Claims 11-14 were withdrawn from further consideration by the examiner in Paper No. 8. Claims 1-10 are being examined on their merits.

Withdrawn Rejections/Objections

1. All rejections and objections made in the office action mailed on 25 May 2001 (Paper No. 8) are withdrawn.

Claims Rejections – 35 U.S.C. 101/112

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-10 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility.

3. Claims 1-10 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

On page 19, section IV Utility, of the instant specification, applicants assert that the claimed method provides an advantage over previous methods for constructing and screening combinatorial compound libraries. The asserted advantage "*is that the tag directs and encodes the synthesis of the compound to which it is covalently attached (not merely reporting on the synthetic history of individual compounds), the tag can be used to create library subpopulations based on hybridization, the types of compounds that are synthesized are not limited to polypeptides and polynucleotides, the number of compounds that may be produced far exceeds that of traditional combinatorial libraries and the tag is a DNA molecule which can be amplified biochemically and inproved by genetic recombination, and in vitro evolution.*"

Applicant's claimed method must satisfy 35 USC 101 and 112 (1) as defined by the statute and case law. In this regard, Applicant is directed to MPEP 2107, 2107.01, and 210.02, which provide guidelines for determining the criteria for satisfying utility and enablement.

Initially it is noted that merely disclosing the ability to make a compound or compounds (e.g. a library) is in itself insufficient utility to satisfy either 35 USC 101 or 112, first paragraph as determined by the U.S. Supreme Court. (e.g. See *Brenner v. Manson,* 383 U.S. 519, 148 USPQ 689 (1966)).

According to the text of 35 USC sec. 101, an invention must be "*useful*". Our reviewing courts have applied the labels, "*specific utility*" (or "*practical utility*") to refer to this aspect of the "*useful invention*" requirement of sec. 101. (Nelson v. Bowler, 626 F.2d 853, 206 USPQ 881, 883 (CCPA 1980)). In Nelson, the court characterized "*specific utility*" (or "*practical utility*") as "*a shorthand way of attributing real-world value to claimed subject matter. In other words, one*

skilled in the art can use a claimed discovery in a manner which provides some immediate benefit to the public." (Id. at 856).

The claimed method of tag-directed synthesis of a plurality of compounds does not, without further research and experimentation, provide an immediate benefit to the public.

Rather, the claimed method merely provides a means of making a plurality of compounds that may or may not have any utility. Any benefit to the public (to one of ordinary skill in the art) is speculative. One of ordinary skill in the art could, hypothetically, use the claimed method to make a library of molecules and it is possible that one of those molecules could have some utility. Applicants assert that virtually any type of molecule can be made by the method but, without further guidance or experimentation, one of ordinary skill would not know what utility any of the compounds may or may not have. Consequently, the utility of the claimed method is left for one using the method to determine.

Indeed, many research tools such as telescopes, gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility. (See USPTO Utility Guidelines, page 12.)

However, inventions that have a specifically identified utility must be distinguished from those whose utility requires further research to identify or reasonably confirm. (Id.) Research tools (such as gas chromatographs, screening assays, etc.) are useful in the sense that they can be used in conjunction with other method steps to evaluate materials other than themselves or to arrive at some result. The claimed method is not a research tool in this sense. Rather, it is the subject of basic research, whose usefulness or lack thereof has yet to be established.

In the absence of an asserted specific utility, the "*useful*" requirement may be established by reference to a well-established utility. A "*well-established utility*" is a "*specific utility*" which is well known, immediately apparent and implied by the specification based on the disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art.

The claimed method is not supported by a well-established utility, however, because neither the specification as filed nor any art of record discloses or suggests any property or activity for the compounds to be made such that another non-asserted utility would be well established for the compounds (and therefore the method).

Accordingly, the total lack in the specification of teaching regarding what compounds made by the claimed method may possess a utility and what that utility may be necessarily places undue experimentation on the public to determine assay or assays for screening the resulting library for a property of value to the public.

Claims Rejections – 35 U.S.C. 112, first paragraph

4. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention without undue experimentation.

Several factors are to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any required experimentation is "undue." These factors include:

1) the breadth of the claims
2) the nature of the invention
3) the state of the prior art
4) the level of one of ordinary skill
5) the level of predictability in the art
6) the amount of direction provided by the inventor
7) the existence of working examples
8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claimed method encompasses the chemical synthesis of any compound whatsoever, including any class of biological molecule (e.g. peptide, oligonucleotide, carbohydrate, sterol, sphingolipid, prostaglandin, leukotriene, porphyrin, and polyketides), any inorganic compound, and any non-biological organic molecule of any size or complexity with no limitation on the identities, numbers, or locations of any carbon atom or hetero-atom. The claims encompass any chemistry for achieving the synthesis of any molecule, including solid phase, solution phase,

solid support / liquid phase, organic solvent, aqueous solvent, and immiscible, two-solvent-based synthesis methods.

The nature of the invention is such that a DNA tag directs the synthesis of the molecules being synthesized by a variety of methods.

The state of the prior art was such combinatorial chemical libraries of limited numbers of structural classes by various methods were known in the art (See Terret, N.K. "*Combinatorial Chemistry*," Oxford University Press, 1998, pp. 4, 8, 26, 64, 96, and 102 for examples of limitations, requirements, and predictability of combinatorial library synthesis). No library synthesis directed by nucleic acid tags was known in the art (other than replication, transcription, and translation systems, which synthesize DNA or RNA using DNA as a template or peptides using RNA as a template).

The level of predictability in the art with respect to combinatorial library synthesis was variable, depending on the molecules being synthesized and the chemical methods used (see Terret, with specific passages highlighted for applicants' convenience). The level of predictability was highest for peptide and oligonucleotide chemistry, while the synthesis of carbohydrate and other non-peptide and non-oligonucleotide molecules ranged from less predictable to entirely unpredictable. Because there were no examples in the prior art of using oligonucleotides to direct the synthesis of combinatorial libraries, methods involving such steps would be more unpredictable than synthetic methods not involving oligonucleotide tag-directed synthesis.

The specification provides no working examples of the claimed method and provides only references to known method of library synthesis that do not involve tag-directed synthesis in way of guidance. The specification does provide some general guidance as to possible strategies for using the claimed method but the specification lacks specific guidance that would allow one of ordinary skill to use the claimed method to make any particular type of library.

One of ordinary skill in the art would not be able to use the presently claimed method commensurate in scope with the present claims, even after considerable experimentation because the claims are universally broad and encompass molecules that cannot be synthesized and molecules for which the synthetic chemistry will take years or decades to perfect. Even within the limited scope of synthesizing peptide or oligonucleotide libraries, one of ordinary skill would

be required to perfect every detail of actually achieving tag-directed synthesis. One would be required to experimentally determine annealing conditions that would simultaneously allow specific hybridization for many diverse sequences with diverse melting temperatures. One would be required to develop synthetic chemistry methods that are compatible with whatever form of tag (including any modified oligonucleotides as defined in the specification) so that the tag is not degraded and does not interfere with synthesis, for example.

Consequently, one of ordinary skill in the art would not be able to use the presently claimed method without undue experimentation.

Claims Rejections – 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-5 and 8-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claim 1, the term "*nucleic acid tags*" does not provide one of ordinary skill in the art a means of determining the metes and bounds of the claimed method. It is not clear if the term encompasses "*oligonucleotide analogs*" as defined in the specification.

B. In claims 1 and 9, the term "*chemical reaction site*," as defined in the specification, does not provide one of ordinary skill in the art a means of determining the metes and bounds of the claimed invention. Page 9 of the specification defines "*chemical reaction site*" as "*a chemical component capable of forming a variety of chemical bonds including, but not limited to...*" This definition provides no means for determining the metes and bounds of the claimed invention because any "*component*" of any compound is "*capable of forming a variety of chemical bonds.*" Consequently, one of ordinary skill in the art would not have any structural or functional definition to distinguish what molecules are encompassed by the claim.

C. In claim 1, it is not clear what a "*reagent-specific compound intermediate*" is. Clarification is requested.

D. In claim 1, it is not clear if each of the nucleic acid tags are reacted with the same reagent or if each tag is reacted with the same reagent, or if the same reagent may be used with more than one tag. Clarification is requested.

E. In claim 2, the term "*oligonucleotide analog*" not provide a means for determining the metes and bounds of the claim. The term is defined on page 8 of the specification as "*a nucleic acid that has been modified and which is capable of some or all of the biological activities of the oligonucleotide form which it was derived.*" One of ordinary skill would have no way of knowing what degrees of modification are encompassed by the term or what "*biological activities*" are encompassed. Base-pairing, for example can be reasonably be considered a physical property rather than a biological property.

F. In claim 3, it is not clear what the method is making. The preamble recites "*for use in forming a plurality of oligomers with different subunit sequences.*" Page 9 of the specification defines "*subunit oligomers*" as typically having 3 to 20 residue positions "*at which the subunit assumes one of a plurality of possible forms, e.g. different nucleic acid or amino acid side chains.*" Consequently, it is clear that nucleic acids and peptides are encompassed by the claim, but is not possible to determine what other types of molecules are included or excluded form the scope of the claim. Also, it is not clear what the metes and bounds of "*subunit*" are.

G. In claim 4, the term "*small molecules*" is not clear because the metes and bounds of the claim cannot be determined. It is not clear what molecular weight or molecular volume are to be used to differentiate between molecules that are small and those that are not.

H. In claim 4, the terms "*small molecules with different chemical sequences*" is not clear. The definition on page 9 of the specification provides no structural or functional standards that can be used to determine the metes and bounds of the claim. The definition states that they are "*usually non-oligomeric*" so the term "*chemical sequence*" is difficult to interpret. In the art, "*sequence*" is associated with an oligomeric molecule and not with non-oligomeric molecules. It is not possible to interpret the meaning of "*sequence*" for non-oligomeric (non-linear) molecules.

I. Claims 1 and 5 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting

to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: relationships between the sequences in the nucleic acid tags and the reactions that result in the directed synthesis of a plurality of compounds. It is not clear what relationships are required and responsible for the synthesis of different molecules onto the different tags or how the different reactions taking place on different tags are cooperatively related to the sequences present on the tags.

J. In claim 8, it is not clear if the subpopulation nucleic acid tags to be used to carry out the method of claim 1 still have synthesized compounds attached or what method steps might be used to "*yield a subpopulation of nucleic acid tags.*" Presumably, the tags yielded in claim 8 cannot be used in the method of claim 1 if they are still attached to the compounds synthesized on them, but the claim does not recite method steps for removal of the tags from the synthesized compounds. If the compounds are not removed from the tags, it is not clear how the method of claim 1 can be performed using the tags.

K. Claims 9 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: method steps that provide a means for "*adding a chemical reaction site.*"

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Tomas Friend** at telephone number **(703) 308-4548**. The examiner can normally be reached on Monday, Tuesday, Friday, and Saturday 8:00-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat can be reached on (703) 308-2439. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-2742.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist at (703) 308-1235.

J. Venkat

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Tomas Friend, Ph.D.
03 April 2002